

### ***Amendments to the Claims***

This listing of claims will replace all prior versions, and listings of claims in the application.

1. (Original) A method of diagnosing or prognosticating Alzheimer's disease in a subject, or determining whether a subject is at increased risk of developing said disease, comprising determining a level and/or an activity of

(i) a transcription product of the gene coding for MAL2 protein, and/or

(ii) a translation product of the gene coding for MAL2 protein, and/or

(iii) a fragment, or derivative, or variant of said transcription or translation product,

in a sample obtained from said subject and comparing said level and/or said activity of said transcription product and/or said translation product to a reference value representing a known disease status and/or to a reference value representing a known health status, and said level and/or said activity is varied compared to a reference value representing a known health status, and/or is similar or equal to a reference value representing a known disease status, thereby diagnosing or prognosticating Alzheimer's disease in said subject, or determining whether said subject is at increased risk of developing said disease.

2. (Currently amended) A kit for diagnosing or prognosticating a neurodegenerative disease, ~~in particular Alzheimer's disease,~~ in a subject, or determining

the propensity or predisposition of a subject to develop such a disease, said kit comprising at least one reagent which is selected from the group consisting of

(i) reagents that detect a transcription product of the gene coding for MAL2 protein and

(ii) reagents that detect a translation product of the gene coding for MAL2 protein, whereby the diagnosis or prognosis or determination of the propensity or predisposition to develop ~~Alzheimer's~~ said neurodegenerative disease is determined by the steps of:

[[ (i) ] ] (a) detecting in a sample obtained from said subject a level, or an activity, or both said level and said activity of a transcription product and/or of a translation product of a gene coding for MAL2, and

[[ (ii) ] ] (b) comparing said level or activity, or both said level and said activity of a transcription product and/or of a translation product of a gene coding for MAL2 to a reference value representing a known health status and/or to a reference value representing a known disease status, and said level, or activity, or both said level and said activity, of said transcription product and/or said translation product of a gene coding for MAL2 is varied compared to a reference value representing a known health status, and/or is similar or equal to a reference value representing a known disease status.

3. (Currently amended) A modulator of an activity and/or of a level of at least one substance which is selected from the group consisting of

(i) a gene coding for MAL2 protein, ~~and/or~~

- (ii) a transcription product of the gene coding for MAL2 protein, ~~and/or~~
- (iii) a translation product of the gene coding for MAL2 protein, and ~~and/or~~
- (iv) a fragment, or derivative, or variant of (i) to (iii).

4. (Currently amended) A recombinant, non-human animal comprising a non-native gene sequence coding for MAL2 or a fragment, or a derivative, or a variant thereof, said animal being obtainable by:

- (i) providing a gene targeting construct comprising said gene sequence and a selectable marker sequence, [[and]]
- (ii) introducing said targeting construct into a stem cell of a non-human animal, [[and]]
- (iii) introducing said non-human animal stem cell into a non-human embryo, [[and]]
- (iv) transplanting said embryo into a pseudopregnant non-human animal, [[and]]
- (v) allowing said embryo to develop to term, [[and]]
- (vi) identifying a genetically altered non-human animal whose genome comprises a modification of said gene sequence in both alleles, and
- (vii) breeding the genetically altered non-human animal of step (vi) to obtain a genetically altered non-human animal whose genome comprises a modification of said endogenous gene, wherein said modification-~~disruption~~ results in said non-human animal exhibiting a predisposition to developing symptoms of a neurodegenerative disease or related diseases or disorders.

5. (Currently amended) A method of diagnosing or therapy for treating neurodegenerative diseases, comprising Use of the recombinant, non-human animal according to claim 4 for screening, testing, and validating compounds, agents, and modulators using the genetically altered non-human animal of claim 4, in the development of diagnostics and therapeutics to treat neurodegenerative diseases, in particular Alzheimer's disease.

6. (Currently amended) ~~An assay~~ A method for screening for a modulator of neurodegenerative diseases, ~~in particular Alzheimer's disease,~~ or related diseases or disorders of one or more substances selected from the group consisting of

- (i) a gene coding for MAL2 protein, ~~and/or~~
- (ii) a transcription product of the gene coding for MAL2 protein, ~~and/or~~
- (iii) a translation product of the gene coding for MAL2 protein, and ~~and/or~~
- (iv) a fragment, or derivative, or variant of (i) to (iii),

said method comprising:

- (a) contacting a cell with a test compound;
- (b) measuring the activity and/or level of one or more substances recited in (i) to (iv);
- (c) measuring the activity and/or level of one or more substances recited in (i) to (iv) in a control cell not contacted with said test compound; and comparing the levels and/or activities of the substance in the cells of step (b) and (c), wherein an alteration in the activity and/or level of substances in the contacted cells indicates that the test compound is a modulator of said diseases or disorders.

7. (Currently amended) A method of screening for a modulator of neurodegenerative diseases, ~~in particular Alzheimer's disease~~, or related diseases or disorders of one or more substances selected from the group consisting of

- (i) the gene coding for MAL2 protein, ~~and/or~~
- (ii) a transcription product of the gene coding for MAL2 protein, ~~and/or~~
- (iii) a translation product of the gene coding for MAL2 protein, and ~~and/or~~
- (iv) a fragment, or derivative, or variant of (i) to (iii),

said method comprising:

(a) administering a test compound to a test animal which is predisposed to developing or has already developed symptoms of a neurodegenerative disease or related diseases or disorders in respect of the substances recited in (i) to (iv);

(b) measuring the activity and/or level of one or more substances recited in (i) to (iv) ;

(c) measuring the activity and/or level of one or more substances recited in (i) or (iv) in a matched control animal which is predisposed to developing or has already developed symptoms of a neurodegenerative disease or related diseases or disorders in respect to the substances recited in (i) to (iv) and to which animal no such test compound has been administered; and

(d) comparing the activity and/or level of the substance in the animals of steps ~~step~~ (b) and (c), wherein an alteration in the activity and/or level of substances in the test animal indicates that the test compound is a modulator of said diseases or disorders.

8. (Original) The method according to claim 7 wherein said test animal and/or said control animal is a recombinant animal which expresses MAL2, or a fragment, or a derivative, or a variant thereof, under the control of a transcriptional control element which is not the native MAL2 gene transcriptional control element.

9. (Currently amended) An assay for testing a compound, ~~preferably for screening~~ or a plurality of compounds to determine the degree of binding of said compounds to MAL2 protein, or to a fragment, or derivative, or variant thereof, said assay comprising ~~the steps of:~~

(i) adding a liquid suspension of said MAL2 protein, or a fragment, or derivative, or variant thereof, to a plurality of containers;

(ii) adding a detectable, ~~in particular a fluorescently labelled compound or a plurality of detectable, in particular fluorescently labelled compounds~~ to be screened for said binding to said plurality of containers;

(iii) incubating said MAL2 protein, or said fragment, or derivative, or variant thereof, and said detectable, ~~in particular fluorescently labelled compound or detectable, in particular fluorescently labelled compounds~~;

(iv) measuring amounts of detectable compound or compounds ~~preferably the fluorescence~~ associated with said MAL2 protein, or with said fragment, or derivative, or variant thereof; and

determining the degree of binding by one or more of said compounds to said MAL2 protein, or said fragment, or derivative, or variant thereof.

10. (Currently amended) Use of The method of claim 1, comprising determining a level and/or activity of a protein molecule of SEQ ID NO:1, said protein molecule being a translation product of the gene coding for MAL2, or a fragment, or derivative, or variant thereof, as a diagnostic target for detecting Alzheimer's disease.

11. (Currently amended) The method of claim 10, wherein said screening is for identification of a modulator of Use of a protein molecule of SEQ ID NO: 1, said protein molecule being a translation product of the gene coding for MAL2, or a fragment, or derivative, or variant thereof, as a screening target for reagents or compounds preventing, or treating, or ameliorating Alzheimer's disease.

12. (Currently amended) A method for detecting the pathological state of a cell in a sample obtained from a subject, comprising immunocytochemical staining of said cell with Use of an antibody specifically immunoreactive with an immunogen, wherein said immunogen is a translation product of a gene coding for MAL2, SEQ ID NO: 1, or a fragment, or derivative, or variant thereof, for detecting the pathological state of a cell in a sample obtained from a subject, comprising immunocytochemical staining of said cell with said antibody, wherein an altered degree of staining, or an altered staining pattern in said cell compared to a cell representing a known health status indicates a pathological state of said cell which relates to a neurodegenerative disease Alzheimer's disease.

13. (New) The kit of claim 2, wherein said neurodegenerative disease is Alzheimer's disease.

14. (New) The kit of claim 2, wherein said translation product is a protein molecule of SEQ ID NO: 1, said protein molecule being a translation product of the gene coding for MAL2, or a fragment, or derivative, or variant thereof.

15. (New) The method of claim 5, wherein said neurodegenerative disease is Alzheimer's disease.

16. (New) The method of claim 6, wherein said neurodegenerative disease is Alzheimer's disease.

17. (New) The method of claim 7, wherein said neurodegenerative disease is Alzheimer's disease.

18. (New) The assay of claim 9, wherein said detectable compound is fluorescently labeled.

19. (New) The method of claim 12, wherein said neurodegenerative disease is Alzheimer's disease.